REMARKS

Claims 2, 3, 9, 12-17, 20, 21 and 25 were rejected. Claims 1, 10, 18, 19, 22, 23 and 24 have been amended. Support for the newly amended claims can be found throughout the specification. More specifically, the definition of bisphosphonate from claim 13 and the definition of aromatase inhibitor from claim 17 has been incorporated into the independent claims.

35 U.S.C. 112, first paragraph and second paragraph rejections

Claims 2 and 3 were rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertain, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. In addition, claims 2 and 3 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2 and 3 have been canceled and therefore, Applicants respectfully request these two rejections be withdrawn from consideration.

Claims 18-25 were rejected under 35 U.S.C. 112, first paragraph, because while the specification enables for the treatment of bone loss in patients suffering from an estrogen dependent disorder, the specification does not reasonably provide enablement for the prevention of bone loss as recited in claims 18-25. Applicants have amended these claims so that the reference to prevention of bone loss is removed. The claims now define methods of treatment.

35 U.S.C. 102(b) Rejection

Claims 1, 9-11, 12, 14-16, 18-20, 24 and 25 were rejected under 35 U.S.C. 102(b) as being anticipated by Freyer et al.. Applicants disagree.

Since claims 9, 12, 14-16, 20 and 25 have been cancelled, Applicants respectfully request the 35 U.S.C. 102(b) rejection be withdrawn from consideration.

The present set of claims recite a combination comprising 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, also known as zoledronic acid, or a pharmaceutically acceptable salt thereof, with 4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile, also known as letrozole, or a pharmaceutically acceptable salt thereof; methods of treatment and packages.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As stated by

the Examiner in the Official Action of October 2, 2007, Freyer does not teach specifically zoledronic acid as the bisphosphonate or letrozole as the aromatase inhibitor, see fourth full paragraph on page 12 of the Official Action. Therefore, Freyer et al. does not teach each and every element as set forth in the claims. Applicants request that the 35 U.S.C. 102(b) rejection be withdrawn.

35 U.S.C. 103(a) Rejection

Claims 1 and 9-25 were rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Reid (N. Engl. J. Med., 2002) and Iqbal (Expert Opin. Pharmacother.). The Examiner argues it would have been obvious to one of ordinary skill in the art at the time of the invention to have combined the methods of treatment as taught by Freyer et al., using specifically zoledronic acid as the bisphosphonate and letrozole as the aromatase inhibitor as taught by Iqbal because it is common practice among one of ordinary skill in the art to select the one of the most active analogs in a family of drugs to achieve the most promising results.

Claims 9 and 10 were rejected under 35 U.S.C. 103(a) as being unpatentable over Freyer et al. in view of Remington's: The Science and Practice of Pharmacy, 19th Edition, Vol. 1, 1985, pages 806). The Examiner argues that it would have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer and included the medication as package with instructions.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck,* 974 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991). All of the references cited published before the Food and Drug Administration approved zoledronic acid, under the trademark ZOMETA. Therefore, at the time of the publication of Freyer et al. and Iqbal et al. it would not have been common practice or even general knowledge among one of ordinary skill in the art to combine the methods of treatment as taught by Freyer et al. and Iqbal to arrive at the claimed combination. The missing descriptive matter in Freyer et al. and Iqbal et al. is the motivation to use zoledronic acid since zoledronic acid had not been approved yet for the treatment of bone metastases. Furthermore, it would not have been obvious to one of ordinary skill in the art to have combined the aromatase inhibitor and bisphosphonate as taught by Freyer and included the medication as package with instructions since zoledronic acid was not approved for the treatment of bone metastases. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). None of the references cited make clear that the missing descriptive matter is necessarily present and such missing descriptive matter

would not have been recognized by a person of ordinary skill. Therefore, the recited combination, methods of treatment and packages as defined in the present set of claims are nonobvious over the prior art.

Example 6, starting on page 50 of the specification describes the effectiveness of intravenous administration of zoledronic acid in preventing the bone loss and reduction of mechanical properties induced by aromatase inhibition or surgical ovariectomy in rats. The results showed a single iv injection of 0.8 μg/kg zoledronic acid delayed bone loss significantly for 24 weeks in patients treated with letrozole with the highest dose being full protective over the entire 24-week duration of the study, page 51 lines 6-10 of the specification. The findings of this study were summarized on page 52 of the specification:

> Discussion: Our data indicates for the first time that in rats, Zol dose-dependenly protects agains cancellous bone loss, corical thinning and reduction of bone strength induced by daily oral letrazole, at a dose of 20μg/kg, fully protects against letrazole induced bone loss for at least 24 weeks.

None of the cited references described the unexpected results found by combining letrazole with zoledronic acid. Example 6 is relevant to the 35 U.S.C. 103(a) rejection because the Example supports the subject matter recited in the claims. Applicants argue that the unexpected beneficial results as described in the present specification support the argument that the claims are non-obvious over the cited prior art. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

The claimed invention is non-obvious over the cited references because the references to do not teach or suggest or provide the requisite motivation for a person of ordinary skill in the art to make the claimed invention. Applicants respectfully request the obviousness rejection be withdrawn from consideration. Entry of this Response is respectfully requested.

Respectfully submitted,

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